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International application number: PCT/US04/043979

International filing date: 23 December 2004 (23.12.2004)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/531,954
Filing date: 23 December 2003 (23.12.2003)

Date of receipt at the International Bureau: 09 February 2005 (09.02.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

World Intellectual Property Organization (WIPO) - Geneva, Switzerland
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APPLICATION NUMBER: ***60/531,954***
FILING DATE: ***December 23, 2003***
RELATED PCT APPLICATION NUMBER: ***PCT/US04/43979***

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17157 U.S. PTO
122303

Docket Number: 225629

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53(c).

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17302 U.S. PTO
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122303

☐ *Additional inventors are being named on the separately numbered sheets attached hereto.*

TITLE OF THE INVENTION (280 characters max)

PROPOFOL ANALOGS, PROCESS FOR THEIR PREPARATION, AND METHODS OF USE

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ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification *Number of Pages:* 26
(including any claims and abstract)
☐ Drawings *Number of Sheets:*
☒ Application Data Sheet. See 37 CFR 1.76

☐ Power of Attorney
☐ Assignment
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☒ Applicant claims small entity status. See 37 CFR 1.27.
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Provisional Transmittal (Revised 10/1/03)

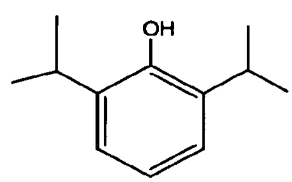
PROPOFOL ANALOGS, PROCESS FOR THEIR PREPARATION, AND METHODS OF USE

FIELD OF THE INVENTION

[0001] The present invention relates to derivatives of propofol. More particularly, the invention relates to para-substituted dialhylphenol propofol compounds, processes for their preparation, and pharmaceutical compositions containing them.

BACKGROUND OF THE INVENTION

[0002] Propofol (2,6-diisopropylphenol, formula I), is a short-acting hypnotic agent, effective for induction and maintenance of anesthesia (see, e.g., Rees et al., *Annu. Rep. Med. Chem.*, *31*, 41-50 (1996), and Trapani et al., *Curr. Med. Chem.*, *7*, 249 (2000)). Propofol also is used for intravenous (IV) sedation by target-controlled infusions (see, e.g., Leitch, *Br. Dent. J.*, *194*, 443 (2003)).



(I)

[0003] Induction of anesthesia with propofol is rapid, and maintenance can be achieved by continuous infusion or by intermittent bolus doses. Propofol is becoming the anesthetic of choice for ambulatory surgery in outpatients. Its greatest advantage is rapid recovery, even after long periods of anesthesia. A particularly low incidence of postoperative nausea and vomiting also has been observed. Disadvantages of propofol include a relatively high incidence of apnea, blood pressure reductions, and pain upon injection.

[0004] A large body of experimental evidence accumulated in the past decade demonstrates that the inhibitory central GABAergic neurotransmission represents an important target in mediating some of the pharmacological actions of propofol. GABA is the major inhibitory neurotransmitter in the vertebrate central nervous system (CNS), whose action is produced by its selective interaction with at least two classes of GABA receptors,

namely $GABA_A$ and $GABA_B$ receptors. While $GABA_B$ receptors are members of the G-protein-linked receptor superfamily and are coupled with K^+ and Ca^{+2} channels, $GABA_A$ receptors are an allosteric inhibitory neurotransmitter-gated ion channel coupled to an integral chloride channel (see, e.g., Sieghart, *Pharmacol. Rev.,* 47, 181 (1995)). $GABA_A$ receptors are composed of a number of phylogenetically related subunits (α1-6, β1-4, γ1-3, δ, ε, ρ1-3), that coassemble to form a pentameric structure which contains a central Cl^- channel. $GABA_A$ receptors express a complex pharmacology. It has been reported that a number of distinct classed of drugs (e.g., benzodiazepines and benzodiazepine-like compounds, beta-carbolines, steroids, barbiturates, alcohols, picrotoxin, and *tert*-butylbicyclophosphorothionate (TBPS)) exert their effects by interacting with specific modulatory sites on this receptor (see, e.g., Barnard et al., *Pharmacol. Rev.*, *50,* 291 (1998)). The effects of propofol on $GABA_A$ channel conductance in rat-cultured hippocampal neurons also have been reported (see, e.g., Eghbali et al., *Eur. J. Pharmacol., 468(2),* 75-82 (2003)). The extracellular domain of the $GABA_A$ receptor contains two GABA binding sites that, when occupied, induce channel opening and subsequent desensitization. The receptor also has binding sites for allosteric modulators, including some general anesthetics.

[0005] It has been observed that the action of general anesthetics may be mediated by a specific subunit of the $GABA_A$ receptor (see, e.g., Sanna et al., *Mol. Pharmacul.*, *47,* 213 (1995)). Indeed, propofol has been shown to produce a strong Cl^- current activation at $\beta1$ homomeric receptors as well as at $\alpha1\beta1$, $\alpha1\beta1\gamma2$, and $\beta1\gamma2$ receptors. Propofol has been shown in electrophysiological assays to allosterically enhance the action of GABA at the $GABA_A$ receptor (see, e.g., Hales et al., *Br. J. Pharmcol.*, *104,* 619 (1991)), and also to prolong inhibitory postsynaptic currents mediated by $GABA_A$ receptors (see, e.g., Orser et al., *J. Neurosci.*, *14,* 7747 (1994)). Propofol can also open the $GABA_A$ receptor ion channel in the absence of GABA, although this usually occurs at higher concentrations of propofol than necessary to potentiate submaximal receptor response of GABA (see, e.g., Jones et al., *J. Pharmacol. Exp. Ther.*, *274,* 962 (1995)). It also has been observed that propofol and analogs thereof produced loss of righting reflex in tadpoles in the action at the $GABA_A$ $\alpha1\beta2\gamma2s$ receptor (see, e.g., Krasowski et al, *J. Pharmacol. Exp. Ther.*, *297,* 338 (2001)).

[0006] Recently, Patel et al., *Br. J. of Pharm.*, *139*, 1005 (2003) reported that propofol activation of the endocannabinoid system, possibly via inhibition of anandamide catabolism, contributes to the sedative properties of propofol, and that fatty acid amide hydrolase could be a novel target for anesthetic development.

[0007] Propofol does not bind at the GABA binding sites. It may bind in a crevice near the extracellular ends of the β subunit M2 and M3 membrane-spanning segments (see, e.g., Williams et al., *J. Neurosci.*, *22*, 7417 (2002)). The effects of propofol on channel kinetics suggest that it stabilizes as a double ligand, pre-open, nonconducing state (see, e.g., Bai et al., *J. Neurosci.*, *19*, 10635 (1999)). At low concentration (0.5 μM), propofol potentiates current induced by submaximal GABA concentrations but does not directly activate $GABA_A$ receptors. At 20-fold higher concentrations, propofol directly activates receptors, causing channel opening in the absence of GABA (see, e.g., Lam and Reynolds, *Brain Res.*, *784*, 178 (1998)).

[0008] Propofol has been used in the treatment of pathologies relating to the presence of free oxygen radicals (see, e.g., U.S. Patent Nos. 5,308,874 and 5,461,080). Propofol has been shown to repair neural damage caused by free oxygen radicals *in vitro* (see, e.g., Sagara et al., *J. Neurochem.*, *73*, 2524 (1999) and Jevtovic-Todorovic et al., *Brain Res.*, *913*, 185 (2001)) and has been used *in vivo* to treat head injury (see, e.g., Kelly et al., *J. of Neurosurgery*, *90*, 1042 (1999)).

[0009] There is evidence suggesting that propofol can protect endothelial cells against oxidative stress by inhibiting eNOS transcription and protein expression (see, e.g., Peng et al., *Chin. Med. J.* (Engl)., *116(5)*, 731-5 (2003)). Moreover, propofol enhances ischemic tolerance of middle-aged hearts, primarily by inhibiting lipid peroxidation (see, e.g., Xia et al., *Cardiovasc. Res.*, *59*, 113 (2003)).

[0010] The search for novel high-affinity ligands for the $GABA_A$ receptor has led to the synthesis of numerous propofol analogs, and to the determination of a structure-activity relationship of propofol binding affinity to $GABA_A$ (reviewed by, e.g., Trapani et al., *Curr. Med. Chem.*, 7, 249 (2000)). The preparation of propofol analogs has been disclosed in, for example, Trapani et al., *J. Med. Chem.*, *41*, 1846 (1998).

[0011] It is possible to modify the molecular structure of propofol in order to optimize all its various activities (e.g., anesthetic, sedative, and anticonvulsant activities) or to yield drugs with more selective actions. Introduction of halogen or benzoyl substituents in the para position of the phenyl group of propofol yielded a series of molecules that inhibit the binding of t-[^{35}S]-butylbicylcophosphorothionate to $GABA_A$ receptors and potentiate GABA-evoked currents at these receptors with an efficacy similar to or higher than that of propofol (see, e.g., Trapani et al., *supra*).

[0012] The only recognized method for delivery of alkylphenols is by intravenous injection in a lipid-based emulsion. After IV administration, propofol is rapidly distributed from the blood into highly perfused areas such as heart, lung, and liver, and to tissues because of its high solubility in lipids. This high solubility enables propofol to cross the blood-brain barrier easily.

[0013] From a clinical viewpoint, several adverse effects have been found in patients undergoing treatment with propofol oil-emulsion. These include pain on injection, apnea, reduction in blood pressure, bradycardia, and excitatory events including convulsions (see, e.g., Langley et al., *Drugs*, *33*, 334 (1988), Rees et al., *Annu. Rep. Med. Chem.*, *31*, 41 (1996), and Sneyd et al., *J. R. Soc. Med.*, *85*, 288 (1992)).

[0014] Recently, Bennett et al., *Bioorg. Med. Chem. Lett.*, *13*, *1971* (2003) disclosed the general anesthetic activity of a series of amino-2,6-dimethoxyphenyl ester derivatives. The new chemicals exhibit improved anesthetic activity in mice relative to propofol.

[0015] Therefore, there is a need for propofol analogs and methods for using propofol analogs to induce general anesthesia, a hypnotic effect, or sleep inducement in a subject. The invention provides such analogs and methods of use. Specifically, the invention provides propofol derivatives that can be used for anesthetic effect generally, and in small doses for hypnotic effect, sedation, or sleep inducement. The new compounds are substantially more active in inducing an anesthetic effect than propofol itself. The result of this increased activity means that the compounds can be used in larger doses for general anesthesia, but in smaller doses to induce a hypnotic effect, sedation, and sleep effect, thereby resulting in a reduction in propofol-related side effects (e.g., cardiovascular side effects). These and other

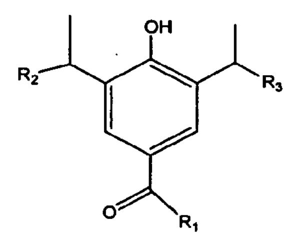
advantages of the invention, as well as additional inventive features, will be apparent from the description of the invention provided herein.

BRIEF SUMMARY OF THE INVENTION

[0016] In accordance with one aspect of the invention, there are provided propofol derivatives, specifically para-substituted dialkylphenol propofol derivatives. In another aspect of the invention, there is provided a method of preparing the above-described dialkylphenol derivatives of propofol. In various embodiments, the invention provides a pharmaceutical composition comprising a propofol derivative as described above and a pharmaceutically acceptable carrier. In still other aspects of the invention, there is provided a method of using propofol derivatives to induce general anesthesia, sedation, and/or hypnotic or sleep effects.

DETAILED DESCRIPTION OF THE INVENTION

[0017] The para-substituted dialhylphylphenol propofol derivatives in accordance with the present invention are represented by Formula (II), as follows:



(II)

wherein,

R_1 is hydrogen, C_1–C_6 alkyl, or C_4-C_{20} aryl, and

R_2 and R_3 are hydrogen, or C_1–C_6 alkyl.

[0018] The following definitions refer to the various terms used above and throughout the disclosure.

[0019] The term "C_1–C_6 alkyl" refers to straight or branched, substituted or unsubstituted, aliphatic groups of 1-6 carbon atoms including, for example, methyl, ethyl, propyl, isopropyl, cyclopropyl, n-butyl, isobutyl, sec-butyl, cyclobutyl, tert-butyl, pentyl, hexyl, and cyclohexyl.

[0020] The term "C_4-C_{20} aryl" refers to an aromatic or heteroaromatic ring including, by way of example, phenyl, naphthgl, furangyl, and thionyl. The aryl ring can be unsubstituted or it can be substituted. Substituents halo (e.g. flouro, chloro, bromo and iodo) C_1–C_6 alkyl

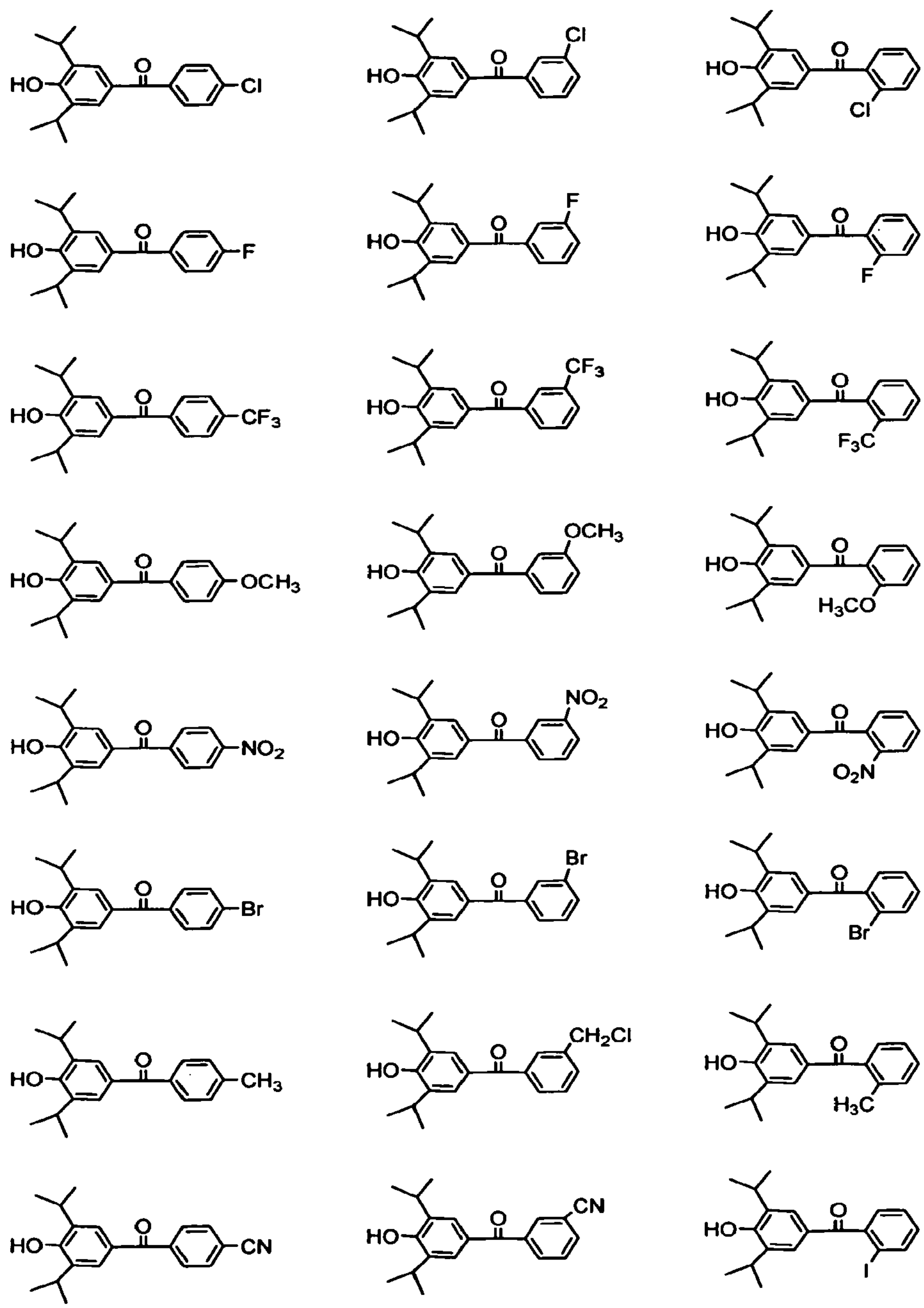
which can be substituted, for example, by halogen, C_1–C_6 alkoxy –NO_2, -CN, anhydride, phenyl amino, carboxyl and alkyl substituted amino. The aryl ring can be substituted with any of one, two, three, four, five or more substituents, depending on the size of the ring. Examples of suitable C_4-C_{20} aryl groups include, for example, 4-chlorophenyl, 3-chlorophenyl, 2-chlorophenyl, 4-trifluoromethylphenyl, 3-trifluoromethylphenyl, 2-trifluoromethylphenyl, 4-methoxyphenyl, 3-methoxyphenyl, 2-methoxyphenyl, 4-nitrophenyl, 3-nitrophenyl, 2-nitrophenyl, 4-cyanophenyl, 3-cyanophenyl, 2-methylphenyl, 4-methylphenyl, 3-chloromethylphenyl, 4-bromomethylphenyl, 2-ethylphenyl, 3-propylphenyl, 2-iodophenyl, 4-iodophenyl, 4-trifluoromethoxyphenyl, 4-butoxyphenyl, 4-biphenyl, 1-naphthalenyl, 2- naphthalenyl, 2-furanyl, 5-nitro-2-furanyl, 2-thiophenyl, 3,4-methylenedioxyphenyl, 2,4-dimethoxyphenyl, 2,6-dimethoxyphenyl, 3,4-dimethyoxyphenyl, 3,5-dimethoxyphenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2,4-dichlorophenyl, 2,6-dichlorophenyl, 3,5-dichlorophenyl, 2,5-bis(trifluoromethyl)phenyl, 3,5-bis(trifluoromethyl)phenyl, 4-chloro-3-nitrophenyl, 5-bromo-2-methoxyphenyl, 2-fluoro-3-trifluoromethylphenyl, 2-fluoro-5-trifluoromethylphenyl, 2-fluoro-6-trifluoromethylphenyl, 3-fluoro-4-trifluoromethylphenyl, 3-fluoro-5-trifluoromethylphenyl, 2,3,4-trifluorophenyl, 2,3,6-trifluorophenyl, 2,4,5-trifluorophenyl, 2,4,6-trichlorophenyl, 2,4-dichloro-5-fluorophenyl, 3,4,5-trimethoxyphenyl, 2,4,5-trifluoro-3-methoxyphenyl, 2,3,4,5-tetrafluorophenyl, pentafluorophenyl, 4,5-diphenyl-imidazol-2-yl, and the like.

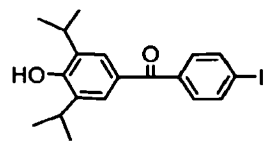
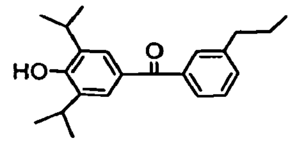
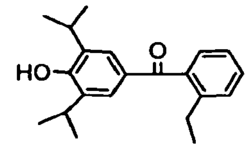
[0021] The term "C_1–C_6 alkoxy" includes the straight or branched aliphatic ether functionalities of 1-6 carbon atoms such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentoxy, hexoxy, cyclohexoxy, and phenoxy.

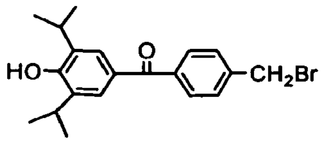
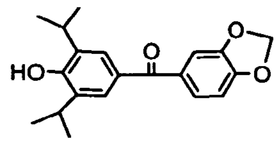
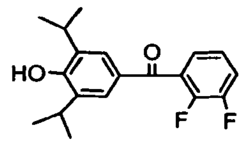
[0022] The compounds of Formula II are useful to induce general anesthesia, hypnosis, sedation and sleep in a subject, particularly in mammals, and most preferably in humans. In preferred emobodiments of the invention, in the compounds represented by Formula II, R_1 is a substituted phenyl, and R_2 and R_3 are C_1-C_4 alkyl. Most preferably, R_3 is a 4-substituted phenyl, and R_2 and R_3 are methyl and ethyl, respectively. Preferred 4-substituted phenyl groups are 4-flourophenyl, 4-chlorophenyl, 4-bromophenyl, 4-triflouromethylphenyl, 4-

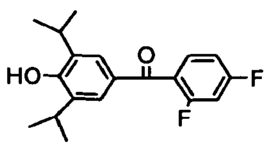
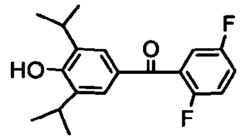
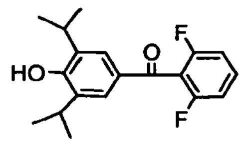
methoxyphenyl, 4-nitrophenyl, 4-cyanophenyl, 4-methylphenyl, 4-iodophenyl, 4-triflouromethoxyphenyl, 4-bromomethylphenyl, 4-dimethylaminophenyl, and 4-biphenyl.

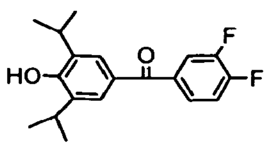
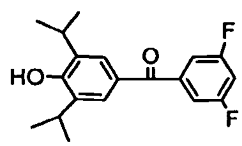
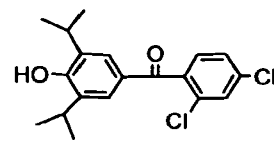
[0023] Preferred embodiments falling within the scope of this invention are as follows:

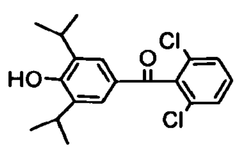
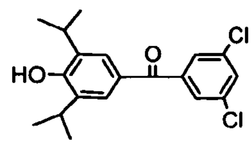
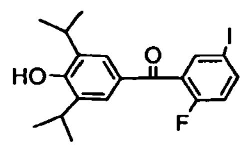


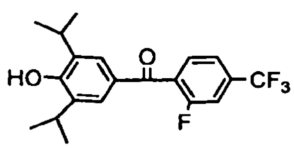
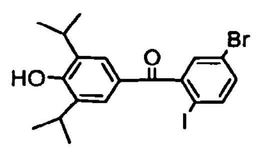
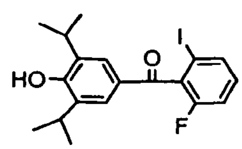




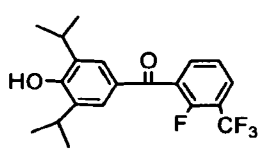
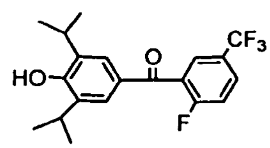
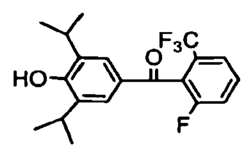




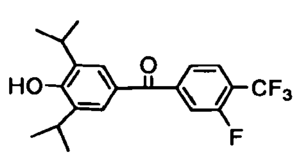
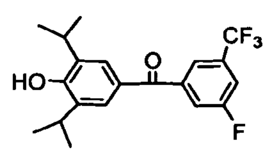
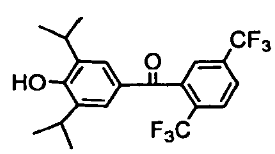




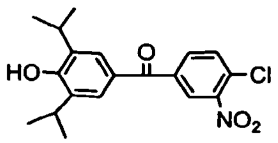
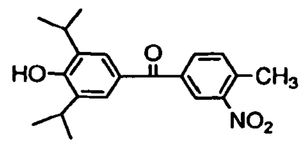
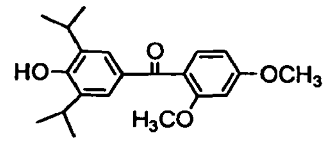




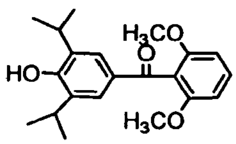
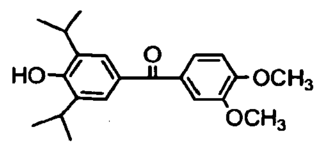
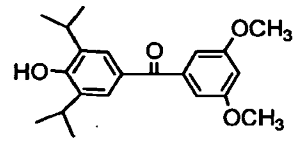




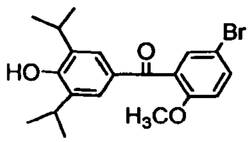
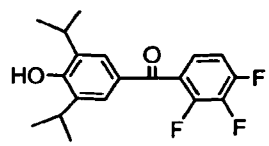
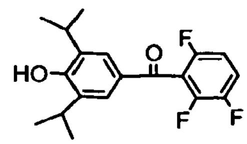




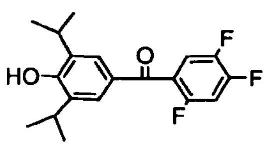
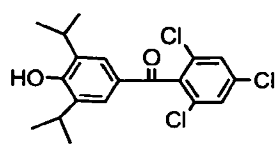
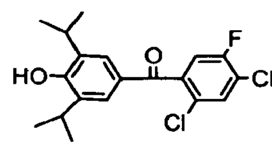




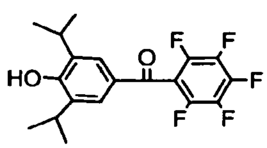
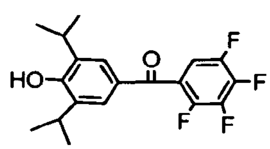
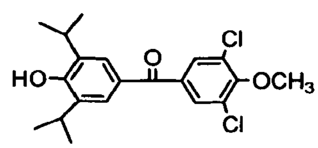




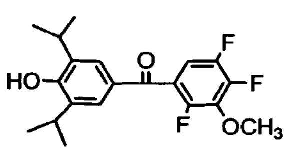
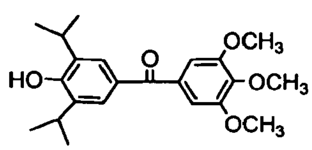
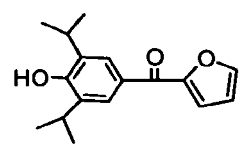




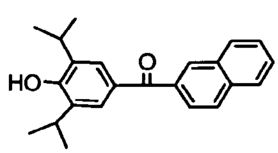
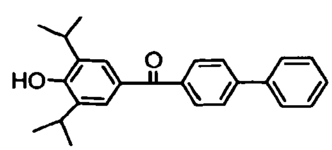
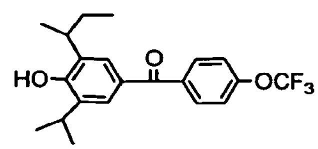




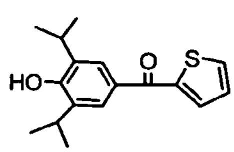
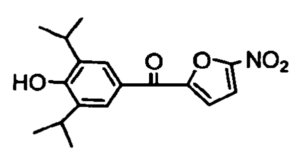
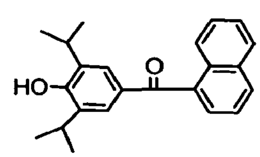




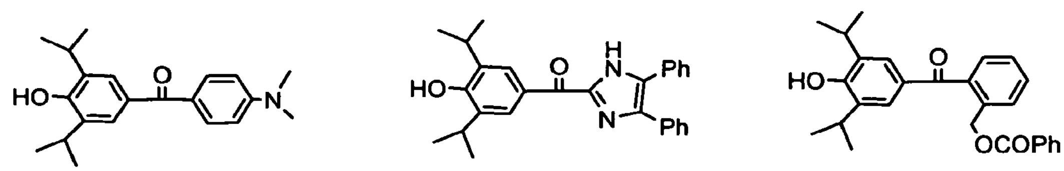




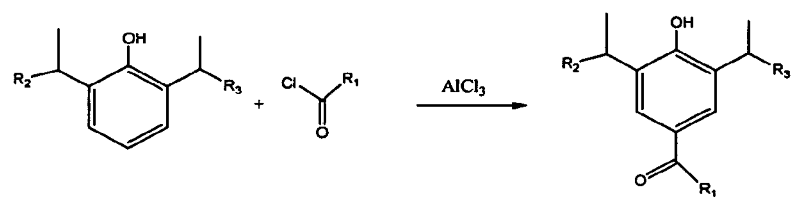






[0024] The preparation of formula II preferably is carried out as illustrated in Scheme 1:

Scheme 1



[0025] The compounds of present invention are prepared as illustrated in Scheme 1. The mixture of 2,6-dialkyl phenol is treated with acyl chloride in the presence of Lewis acid, such as aluminum chloride, titanium tetrachloride, or zinc chloride for 1-24 hours. The reaction can be carried out in either toluene, dichloromethane, or other anhydrous solvent. After reaction, the mixture is quenched with ice water and extracted with organic solvent, such as ether, ethyl acetate, dichloromethane, chloroform, and the like. After removal of organic solvent, the residue can be purified with general flask column chromatography to afford the desired product, and can be accompanied by an ester of the desired product, which can be hydrolyzed by aqueous sodium hydroxide to produce the desired p-substituted 2,6-dialkylphenol.

[0026] The other starting materials employed in the manufacturing method of this invention are known in the art or can be made by methods described in the art. The preparative methods for various 2,6-dialkylphenol derivatives are disclosed in, for example, James and Glen, *J. Med. Chem.*, *23*, 1350 (1980)).

[0027] Thus, in accordance with the invention, para-aryl phenol analogs can be prepared by the reaction of acyl halide with dialkyl phenol in the presence of a Lewis acid, such as aluminum chloride, titanium tetrachloride, zinc chloride, or the like. In general, any aryl acyl halide can be used for the preparation of the present invention. Since aryl acyl halide can be prepared from the corresponding aryl carboxylic acid according to the general procedure in the organic chemistry, many novel compounds can be prepared in accordance with the invention.

[0028] The compounds disclosed herein can be formulated into pharmaceutical compositions for administration to a patient, preferably a human patient. Any of a number of suitable pharmaceutical formulations can be utilized as a vehicle for the administration of the compounds of the invention. Preferably, the inventive compounds are formulated for general pharmaceutical use. Most preferably, the inventive compounds are formulated for use in anesthesia.

[0029] The composition can be administered to a patient by conventional administration methods for anesthetics, such as, for example, oral administration, nasal respiratory administration, bolus injection, intravenous administration by repeated doses or by continuous infusion, rectal administration, vaginal administration, sublingual administration, cutaneous administration, and slow release routes. Preferably, the pharmaceutical composition is administered by continuous infusion. In some embodiments, the pharmaceutical composition can be administered by two or more routes, such as by bolus injection followed by continuous intravenous administration.

[0030] Typically, the compound is mixed with a carrier, diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper, or other container. When the carrier serves as a diluent, it can be a solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments which contain, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

[0031] For oral administration, the active compound of the present invention can be incorporated into suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone, or gelatin.

[0032] Examples of suitable carriers, excipients, and diluents include, for example, lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, saline solution, syrup, methylcellulose, methyl- and propylhydroxybenzoates, talc, magnesium stearate, and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents, or flavoring agents. The compositions can be formulated so as to provide rapid, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

[0033] Preferred compositions for administration by injection include those comprising a novel biologically active analogue as the active ingredient, in association with a surface-active agent (or wetting agent or surfactant), or in the form of an emulsion (e.g., as a water-in-oil or oil-in-water emulsion). Suitable surface-active agents include, in particular, nonionic agents, such as polyoxyethylenesorbitans (e.g., Tween™ 20, 40, 60, 80, or 85), and other sorbitans (e.g., Span™ 20, 40, 60, 80, or 85). Other ingredients can be added, for example, mannitol or other pharmaceutically acceptable vehicles, if necessary.

[0034] The invention also provides compositions comprising propofol derivatives and methods of using such compositions for the *in vivo* delivery of dialkylphenol derivatives in the form of nanoparticles, which are suitable for any aforesaid route of administration.

[0035] The invention also provides methods for the formation of nanoparticles of the inventive compounds by a solvent evaporation technique from an oil-in-water emulsion prepared under conditions of high shear forces (e.g., sonication, high pressure homogenization, or the like). The preparation of nanoparticles from biocompatible polymers

(e.g., albumin) is disclosed in, for example, U.S. Patents 5,916,596, 6,506,405, and 6,537,579.

[0036] Thus, in accordance with the present invention, propofol derivatives are dissolved in a water miscible organic solvent (e.g., a solvent having greater than about 10% solubility in water, such as, for example, ethanol) at a final concentration in the range of about 1%-99% v/v, more preferably in the range of about 5%-25% v/v of the total organic phase. The water miscible organic solvent can be selected from solvents such as, for example, ethyl acetate, ethanol, tetrahydrofuran, dioxane, acetonitrile, acetone, dimethyl sulfoxide, dimethyl formamide, methyl pyrrolidinone, and the like. Alternatively, the mixture of water immiscible solvent with the water miscible solvent is prepared first, followed by dissolution of the pharmaceutically active agent in the mixture.

[0037] Next, a protein (e.g., human serum albumin) is added into the aqueous phase to act as a stabilizing agent for the formation of stable nanodroplets. Protein is added at a concentration in the range of about 0.05 to 25% (w/v), more preferably in the range of about 0.5%-5% (w/v). Unlike conventional methods for nanoparticle formation, no surfactant (e.g. sodium lauryl sulfate, lecithin, tween 80, pluronic F-68, and the like) is added to the mixture. Optionally, a sufficient amount of the first organic solvent (e.g., chloroform) is dissolved in the aqueous phase to bring it close to the saturation concentration. A separate, measured amount of the organic phase (which now contains the pharmacologically active agent, the first organic solvent, and the second organic solvent) is added to the saturated aqueous phase, so that the phase fraction of the organic phase preferably is between about 0.5% and 15% v/v, and more preferably is between 1% and 8% v/v.

[0038] An emulsion is formed by homogenization under high pressure and high shear forces. Such homogenization is conveniently carried out in a high-pressure homogenizer, typically operated at pressures in the range of about 3,000 up to 30,000 psi. Preferably, such processes are carried out at pressures in the range of about 6,000 up to 25,000 psi. The resulting emulsion comprises very small nanodroplets of the nonaqueous solvent containing the dissolved pharmacologically active agent and very small nanodroplets of the protein-stabilizing agent. Acceptable methods of homogenization include processes imparting high

shear and cavitation such as, for example, high-pressure homogenization, high shear mixers, sonication, high shear impellers, and the like.

[0039] The solvent is evaporated under reduced pressure to yield a colloidal system composed of protein-coated nanoparticles of pharmacologically active propofol analog and protein. Acceptable methods of evaporation include, for example, the use of rotary evaporators, falling film evaporators, spray driers, freeze driers, and the like. Thus, a colloidal dispersion system (pharmacologically active agent and protein) in the form of extremely small nanoparticles (e.g., particles in the range of about 10 nm-200 nm diameter) can be sterile-filtered. The preferred size range of the particles is between about 50 nm-170 nm (e.g., about 70 nm, about 100 nm, or about 150 nm), depending on the formulation and operational parameters.

[0040] Colloidal systems prepared in accordance with the present invention can be further converted into powder form by removal of the water, e.g., by lyophilization at a suitable temperature-time profile. The protein (e.g., human serum albumin) itself acts as a cryoprotectant, and the powder is easily reconstituted by addition of water, saline or buffer, without the need to use conventional cryoprotectants such as mannitol, sucrose, glycine, and the like. While not required, it is of course understood that conventional cryoprotectants can be added to the pharmaceutical compositions if so desired.

[0041] The polymeric shell containing solid or liquid cores of pharmacologically active agent allows for the delivery of high doses of the pharmacologically active agent in relatively small volumes. This minimizes patient discomfort at receiving large volumes of fluid and minimizes hospital stay. In addition, the walls of the polymeric shell or coating are generally completely degradable *in vivo* by proteolytic enzymes (e.g., when the polymer is a protein), resulting in no side effects from the delivery system, as compared to current formulations.

[0042] A number of biocompatible materials can be employed in the formation of a polymeric shell. As used herein, the term "biocompatible" describes a substance that does not appreciably alter or affect in any adverse way, the biological system into which it is introduced. Several biocompatible materials can be employed in the practice of the present invention for the formation of a polymeric shell. For example, naturally occurring biocompatible materials such as, for example, proteins, polypeptides, oligopeptides,

polynucleotides, polysaccharides (e.g., starch, cellulose, dextrans, alginates, chitosan, pectin, hyaluronic acid, and the like), and lipids are candidates for such modification.

[0043] As examples of suitable biocompatible materials, naturally occurring or synthetic proteins can be employed. Examples of suitable proteins include, for example, albumin, insulin, hemoglobin, lysozyme, immunoglobulins, α-2-macroglobulin, fibronectin, vitronectin, fibrinogen, casein, and the like, as well as combinations of any two or more thereof. Similarly, synthetic polymers can also be used for preparation of the drug formulation. Examples of suitable synthetic polymers include, for example, polyalkylene glycols (e.g., linear or branched chain), polyvinyl alcohol, polyacrylates, polyhydroxyethyl methacrylate, polyacrylic acid, polyethyloxazoline, polyacrylamides, polyisopropyl acrylamides, polyvinyl pyrrolidinone, polylactide/glycolide, and the like, and combinations thereof.

[0044] These biocompatible materials can also be employed in several physical forms, such as crosslinked or uncrosslinked gels, to provide matrices from which the propofol derivative can be released by diffusion and/or degradation of the matrix. Temperature sensitive materials can also be utilized as the dispersing matrix for the inventive compositions. Thus, for example, a propofol derivative can be injected in a liquid formulation of the temperature sensitive material (e.g., copolymers of polyacrylamides or copolymers of polyalkylene glycols and polylactide/glycolides) which gels at a specific site and provides slow release of the inventive compound.

[0045] Particles of biologic substantially completely contained within a polymeric shell, or associated therewith, prepared as described herein, are delivered neat, or optionally as a suspension in a biocompatible medium. This medium can be selected from water, buffered aqueous media, saline, buffered saline, optionally buffered solutions of amino acids, optionally buffered solutions of proteins, optionally buffered solutions of sugars, optionally buffered solutions of carbohydrates, optionally buffered solutions of vitamins, optionally buffered solutions of synthetic polymers, lipid-containing emulsions, and the like.

[0046] In addition, the polymeric shell can optionally be modified by a suitable agent, wherein the agent is associated with the polymeric shell through an optional covalent bond. Covalent bonds contemplated for such linkages include, for example, ester, ether, urethane,

diester, amide, secondary or tertiary amine, phosphate ester, sulfate ester bonds, and the like. Suitable agents for the optional modification of the polymeric shell include, for example, synthetic polymers such as polyalkylene glycols (e.g., linear or branched chain polyethylene glycol), polyvinyl alcohol, polyhydroxyethyl methacrylate, polyacrylic acid, polyethyloxazoline, polyacrylamide, polyvinyl pyrrolidinone, and the like, phospholipids (e.g., phosphatidyl choline (PC), phosphatidyl ethanolamine (PE), phosphatidyl inositol (PI), sphingomyelin, and the like), proteins (e.g., enzymes, antibodies, and the like), polysaccharides (e.g., starch, cellulose, dextrans, alginates, chitosan, pectin, hyaluronic acid, and the like), chemical modifying agents (e.g., pyridoxal 5'-phosphate, derivatives of pyridoxal, dialdehydes, diaspirin esters, and the like), or combinations of any two or more thereof.

[0047] In one embodiment of the invention, nanoparticles of the inventive compounds can be administered by any acceptable route including, but not limited to, orally, intramuscularly, transdermally, intravenously, through an inhaler or other air borne delivery systems, and the like. When preparing the composition for injection, particularly for intravenous delivery, the continuous phase preferably comprises an aqueous solution of tonicity modifiers, buffered to a pH below 7, more preferably below 6.

[0048] The nanoparticles of this invention can be enclosed in a hard or soft capsule, can be compressed into tablets, or can be incorporated with beverages, food, or otherwise incorporated into the diet. Capsules can be formulated by mixing the nanoparicle with an inert pharmaceutical diluent and inserting the mixture into a hard gelatin capsule of the appropriate size. If soft capsules are desired, a slurry of the compound with an acceptable vegetable oil, light petroleum, or other inert oil can be encapsulated by machine into a gelatin capsule.

[0049] Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable aqueous or organic solvents, or mixtures thereof, and powders. The liquid compositions can contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in sterile pharmaceutically acceptable solvents can be nebulised by use of inert gases. Nebulised solutions can be breathed directly from the

nebulising device, or the nebulising device can be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension, nanoparticle, or powder compositions can be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

[0050] The inventive pharmaceutical compositions can be therapeutically used for any suitable treatment regimens. In this respect, the inventive pharmaceutical compositions can be used for general anesthesia to facilitate surgery, drug or alcohol withdrawal, treatment of tetanus, and other diagnostic or therapeutic interventions. In particular, the inventive pharmaceutical composition can be used to maintain general anesthesia for extended periods (e.g., 24-48 hours) in addicted patients during which drug and/or alcohol withdrawal is provoked. The inventive pharmaceutical composition can be used to maintain general anesthesia for prolonged periods (e.g., days to weeks) in the management of patients with tetanus. The inventive pharmaceutical composition also can be used to render patients sedated and pain-free to facilitate surgical and other therapeutic interventions (e.g., endotracheal mechanical ventilation and wound dressing change in patients with burns) or diagnostic procedures (e.g., endoscopy and imaging techniques) for which loss of consciousness is not required (i.e., "conscious sedation").

[0051] The inventive pharmaceutical compositions also are useful for treatment of migraine headaches. Migraine is a disorder characterized by a persistent headache that may be associated with visual disturbances, nausea, and vomiting. Although the precise cause of a migraine is unknown, it is hypothesized that migraines result from release of neurotransmitters by trigeminal nerves. The trigeminal nerves innervate cerebral blood vessels and inflammation occurs upon neurotransmitter release. Although the mechanism of action of alkyl phenols is not fully understood, propofol is known to be an agonist of $GABA_A$ receptors. Propofol's agonist activity leads to inhibition of neuronal firing which in turn contributes to its anesthetic properties.

[0052] The inventive pharmaceutical composition can be used as an antioxidant. It has been observed that alkylphenols, such as propofol, are very effective antioxidants (see, e.g., Peng et al., *Chin. Med. J. (Engl), 116(5)*, 731 (2003), and Tsuchiya et al., *Am. J. Respir. Crit. Care. Med., 165(1)*, 54 (2002)). Free radicals produced during oxidative stress can react with

proteins, nucleic acids, lipids, and other biological macromolecules, producing damage to cells and tissues. Once formed, free radicals can interact to produce other free radicals and non-radical oxidants such as singlet oxygen and peroxides. A pharmaceutically effective amount of the inventive pharmaceutical composition can be used in treatment regimens for inhibition of oxidation in subjects that are at risk for developing a disease related to oxidative stress, such as cancer. Further, many neurodegenerative diseases such as Alzheimer's disease, Huntington's disease, Parkinson's disease, multiple sclerosis, and others are associated with oxidative stress. Other diseases that are associated with free radicals include ischemic reperfusion injury, inflammatory diseases, stroke, traumatic hemorrhage, spinal cord trauma, cataract formation, gastric ulcers, oxygen toxicity, undesired cell apoptosis, and radiation sickness.

The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope.

EXAMPLE 1

[0053] This example illustrates the preparation of 2,6-diisopropyl-4-(4-fluorobenzoyl)-phenol. To a solution of 2,6-diisopropylphenol (1 g, 5.5 mmol) in 30 mL of toluene were added dropwise 4-flourobenzoyl chloride (1.1 g, 6.1 mmol) and aluminum chloride (0.9 g, 6.6 mmol) at 0 °C. The mixture was then warmed to room temperature and stirred for 7 hours. The mixture was poured into ice-water, and was extracted with ethyl acetate and hexane (1:9). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash silica gel chromatography to afford the desired product as a yellowish solid. The yield was 40%. ^1H NMR (500 MHz, $CDCl_3$) δ 1.28 (d, J=6.8 Hz, 12H), 3.18 (hept, J=6.8 Hz, 2H), 5.34 (br s. 1H), 7.55 (s, 2H), 7.16 (d, d, J=8.6 Hz, 1H), 7.15 (d, J=8.6 Hz, 1H), 7.79 (d, J=8.6 Hz, 1H), 7.81 (d, J=8.6 Hz, 1H); Anal. Calcd for $(C_{19}H_{21}FO_2 + H)^+$ and $(C_{19}H_{21}FO_2 + Na)^+$: 301 and 323. Found: 301 and 323.

EXAMPLE 2

[0054] This example illustrates the preparation of 2,6-diisopropyl-4-(4-trifluoromethylbenzoyl)-phenol. To a solution of 2,6-diisopropylphenol (1 g, 5.5 mmol) in 30 mL of toluene were added dropwise 4-triflouromethyl benzoyl chloride (0.8 ml, 6.1 mmol) and aluminum chloride (0.9 g, 6.6 mmol) at 0 °C. The mixture was then warmed to room

temperature and stirred for 7 hours. The mixture was poured into ice-water, and was extracted with ethyl acetate and hexane (1:9). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash silica gel chromatography to generate the desired product as a yellowish solid. The yield was 42%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (d, J=6.6 Hz, 12H), 3.18 (hept, J=6.6 Hz, 2H), 5.40 (br s. 1H), 7.58 (s, 2H), 7.74 (d, J=8.0 Hz, 2H), 7.85 (d, J=8.0 Hz, 2H); Anal. Calcd for $(C_{20}H_{21}F_3O_2 + H)^+$ and $(C_{20}H_{21}F_3O_2 + Na)^+$: 351 and 373. Found: 351 and 373.

EXAMPLE 3

[0055] This example illustrates the preparation of pharmaceutical compositions comprising an inventive propofol derivative and albumin. 30 mg of 2,6-diisopropyl-4-(4-fluorobenzoyl)-phenol (as prepared in Example 1) was dissolved in 3.0 ml methylene chloride/methanol (9/1). The solution was then added into 27.0 ml of human serum albumin solution (3% w/v). The mixture was homogenized for 5 minutes at low RPM (Vitris homogenizer, model Tempest I.Q.) in order to form a crude emulsion, and then transferred into a high pressure homogenizer (Avestin). The emulsification was performed at 9000-40,000 psi while recycling the emulsion for at least 5 cycles. The resulting system was transferred into a Rotavap, and solvent was rapidly removed at 40 °C at reduced pressure (30 mm Hg), for 20-30 minutes. The resulting dispersion was translucent and the typical average diameter of the resulting particles was in the range 50-220 nm (Z-average, Malvern Zetasizer). The dispersion was further lyophilized for 48 hours. The resulting cake was easily reconstituted to the original dispersion by addition of sterile water or saline. The particle size after reconstitution was the same as before lyophilization. It should be recognized that the amounts, types, and proportions of drug, solvents, proteins used in this example are not limiting in anyway.

EXAMPLE 4

[0056] This example illustrates the formation of nanoparticles of inventive compounds by using cavitation and high shear forces during a sonication process. 20 mg of 2,6-diisopropyl-4-(4-fluorobenzoyl)-phenol (as prepared in Example 1) was dissolved in 1.0 ml methylene chloride. The solution was added to 4.0 ml of human serum albumin solution (5% w/v). The mixture was homogenized for 5 minutes at low RPM (Vitris homogenizer, model Tempest

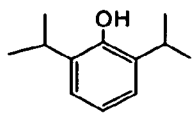
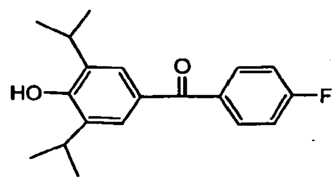
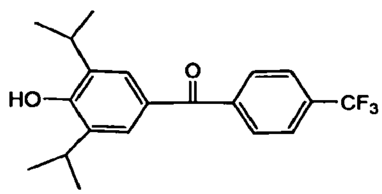
I.Q.) in order to form a crude emulsion, and then transferred into a 40 kHz sonicator cell. The sonication was performed at 60-90% power at 0°C. for 1 minute (550 Sonic Dismembrator). The mixture was transferred into a rotary evaporator, and methylene chloride was rapidly removed at 40°C., at reduced pressure (30 mm Hg), for 20-30 minutes. The typical diameter of the resulting particles was 300-420 nm (Z-average, Malvern Zetasizer).

[0057] The dispersion was further lyophilized for 48 hrs without adding any cryoprotectant. The resulting cake was easily reconstituted to the original dispersion by addition of sterile water or saline. The particle size after reconstitution was the same as before lyophilization.

EXAMPLE 5

[0058] This example illustrates the binding of propofol analogs to the $GABA_A$ receptor. The binding assay of the propofol analogs at the TBOB site on the chloride channel of the $GABA_A$ receptor was carried out according to methods known in the art (see, e.g., Lawrence et al., *J. Neurochem.*, *45*, 798 (1986), and Cole et al., *Life Science, 35*, 1755 (1984)), the results of which are set forth in Table 1. In summary, rat cortical membranes were reconstituted at 0.5 mg protein per mL in 5 mM Tris-HCL/1mM EDTA/ 200 mM KBr buffer at pH 7.5. A 0.5 mL aliquot of the membrane preparation was added to 0.5 mL solution of t-[^{3}H]butylbicycloorthobenzoate ([^{3}H]TBOB) to achieve a final concentration of 4-5 nM TBOB. The reaction tube was incubated at 25°C. with moderate shaking. Specific binding was defined as the difference in labeling of samples incubated with [^{3}H]TBOB only and those incubated in the presence of TBOB. For the inhibitor binding assay, 6-diisopropyl-(4-fluorobenzoyl)-phenol, 2,6-diisopropyl-(4-trifluoromethylbenzoyl)-phenol, and propofol were introduced in 5 μL DMSO prior to adding the membrane preparations and incubation. Median inhibitory concentrations (IC_{50} values) were taken directly from Hill plots. The results of the binding assay are set forth in Table 1.

Table 1. Effect of propofol analogs on the [^{3}H]TBOB binding in the rat cerebral cortex

Chemical structure	**IC_{50}, μM**
	4.86
	1.05
	0.63

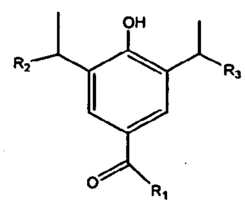
[0059] Thus, this example illustrates that the inventive propofol derivatives exhibit a higher $GABA_A$ binding efficiency than propofol.

<u>EXAMPLE 6</u>

[0060] This example illustrates the preparation of an oil-in-water formulation of the inventive compounds. An aqueous phase is prepared from glycerol (1.00-3.00 % by weight), disodium edetate dihydrate (0.001-0.01% by weight), and water for injections (80-95% by weight). This mixture is stirred and taken to a temperature of approximately 60°C. In parallel to the above, an oil phase is prepared from soybean oil (1.00-10.0% by weight), the inventive compound (1.0–5.0 % by weight) and egg phosphatide (0.5–2.0% by weight) in a vessel. The mixture is stirred at a temperature of approximately 70 to 75°C. until all ingredients are dissolved. Finally, the oil phase and water phase in the mixing vessel are homogenized for 5 minutes at low RPM (Vitris homogenizer, model Tempest I.Q.) in order to form a crude emulsion, and then transferred into a high-pressure homogenizer (Avestin). The emulsification is performed at 9000-40,000 psi while recycling the emulsion until the mean globule size of approximately 250 nM is achieved.

WHAT IS CLAIMED IS:

1. A compound of the formula



wherein
R_1 is hydrogen, C_1–C_6 alkyl, or C_4-C_{20} aryl, and
R_2 and R_3 is C_1–C_6 alkyl.

2. The compound of claim 1, wherein R_1 is C_4-C_{20} aryl, and R_2 and R_3 are methyl.

3. The compound of claim 1, wherein R_1 is C_4-C_{20} aryl, R_2 is hydrogen, and R_3 is methyl.

4. The compound of claim 1, wherein R_1 is C_4-C_{20} aryl, and R_2 and R_3 are ethyl.

5. The compound of claim 1, wherein R_1 is aryl, R_2 is hydrogen, and R_3 is ethyl.

6. The compound of claim 1, wherein R_1 is C_4-C_{20} aryl, R_2 is methyl, and R_3 is ethyl.

7. The compound of claim 1, wherein R_1 is C_4-C_{20} aryl, R_2 is hydrogen, and R_3 is propyl.

8. The compound of claim 1, wherein R_1 is C_4-C_{20} aryl, R_2 is methyl, and R_3 is propyl.

9. The compound of claim 1, wherein R_1 is C_4-C_{20} aryl, R_2 is ethyl, and R_3 is propyl.

10. The compound of claim 1, wherein R_1 is C_4-C_{20} aryl, and R_2 and R_3 are propyl.

11. The compound of claim 2, wherein R_1 is selected from the group consisting of 4-fluorophenyl, 3-fluorophenyl, 2-fluorophenyl, 4-bromophenyl, 3-bromophenyl, 2-bromophenyl, 4-chlorophenyl, 3-chlorophenyl, 2-chlorophenyl, 4-trifluoromethylphenyl, 3-trifluoromethylphenyl, 2-trifluoromethylphenyl, 4-methoxyphenyl, 3-methoxyphenyl, 2-methoxyphenyl, 4-nitrophenyl, 3-nitrophenyl, 2-nitrophenyl, 4-cyanophenyl, 3-cyanophenyl, 2-methylphenyl, 4-methylphenyl, 3-chloromethylphenyl, 2-iodophenyl, 4-iodophenyl, 4-trifluoromethoxyphenyl, 3-propylphenyl, 2-ethylphenyl, 4-bromomethylphenyl, 4-dimethylaminophenyl, 4-biphenyl, 1-naphthalenyl, 2- naphthalenyl, 2-furanyl, 5-nitro-2-furanyl, 2-thiophenyl, 3,4-methylenedioxyphenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2,4-dichlorophenyl, 2,6-dichlorophenyl, 3,5-dichlorophenyl, 2,5-bis(trifluoromethyl)phenyl, 3,5-bis(trifluoromethyl)phenyl, 4-chloro-3-nitrophenyl, 5-bromo-2-methoxyphenyl, 4-methyl-3-nitrophenyl, 2-fluoro-3-trifluoromethylphenyl, 2-fluoro-5-trifluoromethylphenyl, 2-fluoro-6-trifluoromethylphenyl, 3-fluoro-4-trifluoromethylphenyl, 3-fluoro-5-trifluoromethylphenyl, 2,4-dimethoxyphenyl, 2,6-dimethoxyphenyl, 3,4-dimethoxyphenyl, 3,5-dimethoxyphenyl, 3,5-dichloro-4-methoxyphenyl, 2,3,4-trifluorophenyl, 2,3,6-trifluorophenyl, 2,4,5-trifluorophenyl, 2,4,6-trichlorophenyl, 2,4-dichloro-5-fluorophenyl, 3,4,5-trimethoxyphenyl, 2,4,5-trifluoro-3-methoxyphenyl, 2,3,4,5-tetrafluorophenyl, and pentafluorophenyl.

12. The compound of any of claims 3-10, wherein R_1 is phenyl.

13. The compound of any of claims 3-10, wherein R_1 is selected from the group consisting of 4-fluorophenyl, 3-fluorophenyl, 2-fluorophenyl, 4-bromophenyl, 3-bromophenyl, 2-bromophenyl, 4-chlorophenyl, 3-chlorophenyl, 2-chlorophenyl, 4-trifluoromethylphenyl, 3-trifluoromethylphenyl, 2-trifluoromethylphenyl, 4-methoxyphenyl, 3-methoxyphenyl, 2-methoxyphenyl, 4-nitrophenyl, 3-nitrophenyl, 2-nitrophenyl, 4-cyanophenyl, 3-cyanophenyl, 2-methylphenyl, 4-methylphenyl, 3-chloromethylphenyl, 2-iodophenyl, 4-iodophenyl, 4-trifluoromethoxyphenyl, 3-propylphenyl, 2-ethylphenyl, 4-bromomethylphenyl, 4-dimethylaminophenyl, 4-biphenyl, 1- naphthalenyl, 2- naphthalenyl, 2-furanyl, 5-nitro-2-furanyl, 2-thiophenyl, 3,4-methylenedioxyphenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2,4-dichlorophenyl, 2,6-dichlorophenyl, 3,5-dichlorophenyl, 2,5-bis(trifluoromethyl)phenyl, 3,5-bis(trifluoromethyl)phenyl, 4-chloro-3-nitrophenyl, 5-bromo-

2-methoxyphenyl, 4-methyl-3-nitrophenyl, 2-fluoro-3-trifluoromethylphenyl, 2-fluoro-5-trifluoromethylphenyl, 2-fluoro-6-trifluoromethylphenyl, 3-fluoro-4-trifluoromethylphenyl, 3-fluoro-5-trifluoromethylphenyl, 2,4-dimethoxyphenyl, 2,6-dimethoxyphenyl, 3,4-dimethoxyphenyl, 3,5-dimethoxyphenyl, 3,5-dichloro-4-methoxyphenyl, 2,3,4-trifluorophenyl, 2,3,6-trifluorophenyl, 2,4,5-trifluorophenyl, 2,4,6-trichlorophenyl, 2,4-dichloro-5-fluorophenyl, 3,4,5-trimethoxyphenyl, 2,4,5-trifluoro-3-methoxyphenyl, 2,3,4,5-tetrafluorophenyl, and pentafluorophenyl.

14. The compound of claim 1, wherein R_1 is 4-fluorophenyl, and R_2 and R_3 are each methyl.

15. The compound of claim 1, wherein R_1 is 4-trifluoromethylphenyl, and R_2 and R_3 are each methyl.

16. A method for preparing the compound of claim 1, which method comprises reacting an alkylphenol with acyl chloride in the presence of Lewis acid.

17. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier or diluent.

18. The pharmaceutical composition of claim 17, wherein the pharmaceutical composition is for parenteral administration and comprises nanoparticles of an anesthetic inducing effective amount of the compound of claim 1 and a pharmaceutically acceptable anesthetic carrier.

19. A method of inducing sedation, hypnosis and/or sleep effect, or general anesthesia in a patient, which method comprises administering to the patient a therapeutically effective amount of the compound of claim 1.

20. The method of claim 19, wherein said administering is by a method selected from the group consisting of oral administration, nasal respiratory administration, bolus injection, intravenous administration, continuous infusion, rectal administration, vaginal administration, sublingual administration, and cutaneous administration.

21. The method of claim 18, wherein the method of administration is continuous infusion.

ABSTRACT

The invention provides para substituted dialkylphenol derivatives of propofol. The invention further provides pharmaceutical compositions comprising such analogs, methods for preparing such analogs, and methods of using such analogs to induce general anesthesia, sedation, and/or hypnotic or sleep effects in a patient.

Application Data She t

APPLICATION INFORMATION

Application Number::	
Filing Date::	December 23, 2003
Application Type::	Provisional
Subject Matter::	Utility
Suggested classification::	
Suggested Group Art Unit::	
CD-ROM or CD-R?::	None
Number of CD Disks:	
Number of Copies of CDs::	
Sequence Submission?::	
Computer Readable Form (CRF)?::	No
Number of Copies of CRF::	
Title::	PROPOFOL ANALOGS, PROCESS FOR THEIR PREPARATION, AND METHODS OF USE
Attorney Docket Number::	225629
Request for Early Publication?::	No
Request for Non-Publication?::	No
Suggested Drawing Figure::	
Total Drawing Sheets::	
Small Entity?::	Yes
Latin Name::	
Variety denomination name::	
Petition Included?::	No
Petition Type::	
Licensed US Govt. Agency::	
Contract or Grant Numbers::	
Secrecy Order in Parent Appl.?::	No

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Representative Designation::	Registration Number::	Representative Name::

DOMESTIC PRIORITY INFORMATION

Application::	Continuity Type::	Parent Application::	Parent Filing Date::

FOREIGN APPLICATION INFORMATION

Country::	Application Number::	Filing Date::	Priority Claimed

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